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Formulation and Development of Topical Flurbiprofen Emulgel by using Xanthan Gum

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Abstract: *Flurbiprofen is non-steroidal anti-inflammatory drug used for the treatment of rheumatoid arthritis as an autoimmune disease that causes chronic inflammation of the joints. Flurbiprofen is a potent inhibitor of platelets aggregation, which reduce pain, swelling and joint stiffness. The objective of this study was to formulate and evaluate topical flurbiprofen emulgel for the delivery of hydrophobic drugs to systemic circulation. In present work flurbiprofen emulgel was prepared by using liquid paraffin (oil), eucalyptus oil (penetration enhancer) and xanthan gum used as gelling agent. All formulations evaluated for homogeneity, pH, extrudability, spreadability, viscosity, drug content and drug release. In-vitro drug release of emulgel was evaluated by using diffusion cell containing cellophane membrane with phosphate buffer pH 7.4 as the receptor medium. The formulations were optimized by the three factors and two levels Box-Behnken design by using Design-Expert software (version 12). Spreadability of F6 formulation was observed (3.4 cm in diameter) which was more than other formulations. Viscosity of F16 formulation was 3067 cps. Percentage Drug content of F14 (98.61%) has shown more drug content as compared other formulations. In-vitro diffusion studies, the formulations F5, F6, F13, F14 and F16 has shown more than 80 % of drug release for 8 hrs.*

Keywords: *Topical emulgel, flurbiprofen, NSAID, xanthan gum, liquid paraffin and eucalyptus oil.*

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I. Introduction

Skin as a delivery route has been a promising opinion for a long time because skin is easy to access and has a large surface area with vast exposure to the circulatory and lymphatic system [1]. Topical preparation has been the most popular pharmaceutical dosage forms. Skin as a route of drug delivery has gained popularity because it avoids first pass effects, gastrointestinal irritation and metabolic degradation incorporated with oral administration [2].

Emulgel is an emulsion it can be oil-in-water or water in oil type, by mixing gelling agent it is converted in to emulgel. Emulgel is stable and better vehicle for hydrophobic or poorly water-soluble drugs [3]. They have high patient influence since they possess the advantages of both emulsions and gels. Oil-in-water type of emulsion is used to entrap lipophilic drugs, whereas hydrophilic drugs are encapsulated in the reverse water-in-oil type of emulsion. Emulgel shows dual control of the drug release in the formulation e.g. emulsion and gel. Emulsion possess a certain degree of elegance and are easily washed off whenever desired [4]. The delivery of drugs through the skin is a viable administration route for potent, low molecular weight therapeutic agents susceptible to first pass metabolism. Topical drug delivery is called as a localized drug delivery system, drug delivery anywhere in the body through ophthalmic, rectal, vaginal and skin are topical routes. Skin is the most easily approachable organ of human body for topical administration. In the development of transdermal drug delivery system, two criteria are considered: one is achieving adequate flux across the skin and the other is minimizing the lag time in skin permeation [5]. Percutaneous absorption of drugs involves the release of the drug by permeation through skin to reach the target tissue [6].

The major advantage of topical drug delivery system is to avoid the risk of intravenous therapy and gastrointestinal problems like pH changes, presence of enzymes, gastric emptying time, it reduce side effects, improve bioavailability, better patient compliance and easy termination of drug administration are other advantage of the topical drug delivery system. Topical drug delivery is easy and painless. Skin is the largest organ of the human body, providing around 10% of the body mass of an average person, and it covers an average area of 1.7 m^2. Emulgel has a higher aqueous component, which permits better dissolution of drugs, so

the gelling agent in the water phase which converts an emulsion into an emulgel [7].

The present work was to develop a topical emulgel formulation of flurbiprofen, which would help to reduce the gastrointestinal related toxicities integrated with oral administration. It is established that emulgels are superior topical formulation over any other topical formulations, because they have better application property in comparison to gels, creams and ointments [8-9].

II. Materials and Methods

Flurbiprofen was received as a gift sample from Vasudha Pharma Chem Ltd. Andhra Pradesh. Xanthan gum, Span 20, Tween 20, liquid paraffin, glycerin and alpha-tocopherol received from Research fine lab Mumbai. Benzyl alcohol and eucalyptus oil from Merck Life Science Pvt. Ltd. All other chemicals and reagents used were of analytical grade.

A. Method of preparation of Emulgel

1. Drug solution preparation: The exact quantity of flurbiprofen was dissolved in methanol after that a solution of benzyl alcohol and glycerin were added in this solution.

2. Preparation of oil in water emulsion: Oil phase of the emulsion was prepared by dissolving span 20 in liquid paraffin while the aqueous phase was prepared by dissolving tween 20 in purified water. Both the oily and aqueous phases were separately heated up to 70-80°C until complete dissolution then the oily phase was added to the aqueous phase with continuous stirring until cooled to room temperature.

3. Preparation of gel phase: The xanthan gum was weighed accurately and dissolved in water to
   form a gel by neutralizing it with triethanolamine then this gel phase was incorporated in emulsion to form emulgel.

B. Raw material analysis of Flurbiprofen

1. Solubility: Solubility is a chemical property in which solute dissolved in a solvent. It observed when maximum amount of solute dissolved in a solvent at equilibrium. Solubility depends on the nature of drugs as well as the solvent. Polar solutes dissolved in polar solvent and non polar solvents dissolved only non-polar solutes. The nature of the solvent can affect the solubility of drugs. A state of dynamic equilibrium established between these two processes and at this point, the number of solute molecules enters in the solution and becomes equal to the number of particles leaving the solution, concentration of the solute in the solution remains constant at a given temperature and pressure conditions. A solution which have no more capacity to dissolve more solute in the solvent at a given temperature and pressure called saturated solution [10-11].

2. Determination of standard calibration curve of flurbiprofen: 10 mg of flurbiprofen taken and dissolved in 10 ml of methanol, made final volume up to 100 ml in volumetric flask with phosphate buffer (pH 7.4) for the preparation of stock solution. The 10 ml of stock solution was further diluted with phosphate buffer (7.4 pH) in 100ml to get 10µg/ml (working standard). Then 1.0,2.0,3.0,4.0 and 5.0 ml of working standard was taken in 10 ml standard volumetric flask and made up the volume with phosphate buffer to prepare 0.1µg, 0.2µg, 0.3µg, 0.4µg, and 0.5µg drug per ml solution. Then the absorbance was measured in a UV spectrophotometer at 247 nm against phosphate buffer (pH 7.4) as blank [12].

3. Fourier transform infrared spectrophotometer (FTIR): This study was performed to ensure the compatibility between excipients and drug. FTIR studies performed to obtain spectra of pure drug flurbiprofen and liquid FTIR studies performed to check the compatibility of flurbiprofen with different excipients. Spectrum of drug was obtained by using the potassium bromide disc method. Drug and excipients triturated in mortar and pestle and then analyzed. FTIR spectra recorded between 400 and 4000/cm [13-14].

4. Differential scanning calorimeter (DSC): DSC finds many applications in characterizing the materials. It is a thermo analytical technique that needs the amount of heat to increase the temperature of sample. Its quantitative application includes the determination of heat of fusion, and qualitative application is the determination of melting point. It is an important tool in establishing the purity of various preparations [15].

5. X-Ray Diffraction (XRD): X-ray powder diffraction (XRD) is a rapid analytical technique primarily used for phase identification of a crystalline material and can provide information on unit cell dimensions. The analyzed material is finely ground, homogenized, and average bulk composition is determined. 2 θ is the angle between transmitted beam and reflected beam. In any experiment the transmitted and reflected beam can be observed, so 2 θ is an experimentally measurable quantity. But the crystallographic plane cannot be observed. X-ray powder diffraction is most widely used for the identification of unknown crystalline materials (e.g. minerals, inorganic compounds).

III. Experimental design

Design expert® software, version 12, Stat-Ease was used to find correlation between independent and dependent variables. The software itself select the suitable model on the basis of individual parameters generated from regression analysis, such as adjusted R2 value, predicted R2value and p value. At 5% level of significance, analysis of variance was implemented. In design expert the model was screened out by analyzing adjusted R2 value, which has to be <1. The general quadric equation for three independent variables is as follows:

$$Y= \beta_0+X_1\beta_1+X_2\ \beta_2+X_2\ \beta_3+X_1X_2\ \beta_4+X_1X_3\ \beta_5+X_2X_3\beta_6+X^2_1\beta_8\ +X^2_3\beta_8$$

The topical formulations of emulgel were optimized by three factors and two levels Box-Behnken design. Three independent formulation variables were evaluated: a) concentration of polymer b) concentration of oil c) concentration of penetration enhancer. A three factor, two levels Box-Behnken statistical experimental design of the response surface methodology requires 17 runs, of which 5 are the replicates. The % drug release (Y1) and viscosity (Y2) were evaluated as the dependent variables. The one-way analysis variance (ANOVA) was applied to estimate the significance of the model ($P<0.05$) and individual response parameter.

Table1: Independent variables and their corresponding levels for optimization studies

Independent variables		**Levels**	
		-1	+1
Concentration of xanthan gum (gm)	X_1	0.5	1.0
Concentration of liquid paraffin (ml)	X_2	5.0	10.0
Concentration of eucalyptus oil (ml)	X_3	8.0	10.0

Table 2: Box-behnken design for formulation of topical flurbiprofen emulgel

Formulation number	**Factor 1 (X_1)**	**Factor 2 (X_2)**	**Factor 3 (X_3)**
1	0	0	0
2	1	-1	0
3	1	0	-1
4	0	-1	1
5	-1	1	0
6	0	1	1

7	-1	-1	0
8	0	0	0
9	0	0	0
10	0	-1	-1
11	0	0	0
12	-1	0	-1
13	1	0	1
14	0	1	-1
15	-1	0	1
16	1	1	0
17	0	0	0

IV. Evaluation of Emulgel

All Emulgel formulations were evaluated for their appearance, pH, homogeneity, spreadability, viscosity, drug content, in-vitro diffusion studies and compatibility studies.

A. Physical appearance: All emulgel formulations checked visually.

B. Determination of pH: It was determined by using digital pH meter at room temperature [16].

C. Homogeneity: The formulations were tested for their homogeneity by visual appearance, a thin layer of emulgel applied on the glass slide and observed under microscope.

D. Spreadability: Spreadability was measured on the basis of spreading characteristics of emulgel. An excess of emulgel (about 1gm) was taken and kept on glass slide, other slide was put on the ground slide. The emulgel was sandwiched between this slide and another glass slide having the dimension of fixed ground slide. A 100g weight was placed on the top of the two slides for 1 minute to expel air and to provide a uniform film of the emulgel between the slides. Diameter of emulgel was taken after the whole process, distance covered by emulgel was noted in cm. More distance in cm indicates better spreadability [17].

E. Determination of Viscosity: The viscosity of different emulgel formulations was determined at 25°C using a Brookfield viscometer with spindle number 4 at 10 rpm and 100 rpm [18].

F. Extrudability: It was performed to measure the force required to extrude the material from tube. The method was done to determine the correlation between applied shear in the rheogram region and shear rate. To evaluate emulgel formulation for extrudability was based upon the quantity in percentage of emulgel and emulgel extruded from lacquered aluminum collapsible tube by the application of weight in grams required to extrude at least 0.5 - 0.8 cm ribbon of emulgel in 10 seconds. More quantity extruded better is extrudability. The extrudability was calculated by using the following formula [19].

$$Extrudability = \frac{Applied\ weight\ to\ extrude\ emulgel\ from\ tube\ (gm)}{Area\ (cm^2)}$$

G. Drug Content: To confirm uniform formulation of the emulgel, the drug content of the emulgel was determined by dissolving an accurately weighed amount of formulation (1gm) in 100 ml of pH 7.4 phosphate buffer solution. These solutions were transferred to volumetric flasks and dilutions were made with the same buffer solution. After the complete dissolution of sample the resulting solutions were filtered by using whatman filter paper before analyzing the solution in spectrophotometric analysis for flurbiprofen at 247 nm [20].

Drug content = (Concentration × Dilution Factor × Volume taken) × Conversion Factor.

H. In-vitro diffusion studies: Franz diffusion cell (with 15 ml cell volume) was used for the drug release studies. Emulgel (1gm) was applied onto the surface of cellophane membrane evenly. The membrane was kept on the donor part of diffusion cell, both donor and receptor

chamber of diffusion cell clamped by using a clip. The receptor chamber was filled with freshly prepared phosphate buffer solution (pH 7.4) to solubilize the drug. The receptor chamber was kept on magnetic stirrer. The sample (1.0 ml) was collected after one hour interval for 8 hours. All emulgel formulations analyzed for drug release studies by UV visible after appropriate dilutions. The cumulative amount of drug release was determined as a function of time [21].

I. *Stability study:* For stability study, the optimized formulation was subjected to study for the time period of three months at a temperature of 25°C/60% RH for long term stability and 40°C/ 75% RH for accelerated stability [22-23].

V. Results and Discussion

A. Raw material analysis of Flurbiprofen

1. Solubility: Solubility studies were conducted by using different organic solvents. Highest solubility of flurbiprofen was found in acetone, ethanol, methanol and ether.

Table 3: Solubility of flurbiprofen

Solvent	Observation
Water	Insoluble in water
Acetone	Freely soluble in acetone
Ethanol	Freely soluble in ethanol
Methanol	Freely soluble in methanol
Ether	Freely soluble in ether
Acetonitrile	Soluble in acetonitrile

2. Drug- excipient interaction studies: Flurbiprofen was compatible with excipients was studied by FTIR. The FTIR spectra of formulations with excipients reveal no interaction between drug and excipient. Observed peaks were identified and interpreted in the spectra. The FTIR studies from the spectra confirmed the absence of any chemical inter action between the drug and excipients. The FTIR spectra of drug and formulation shown in Figure 1, 2, 3 and 4.

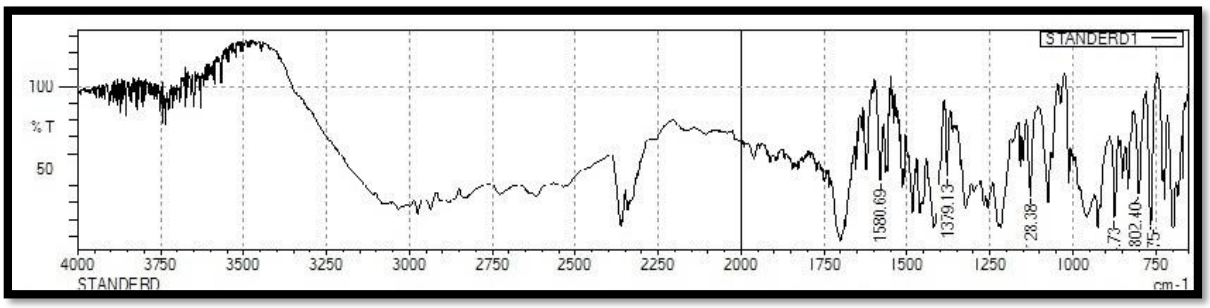

Figure 1: FTIR of flurbiprofen standard

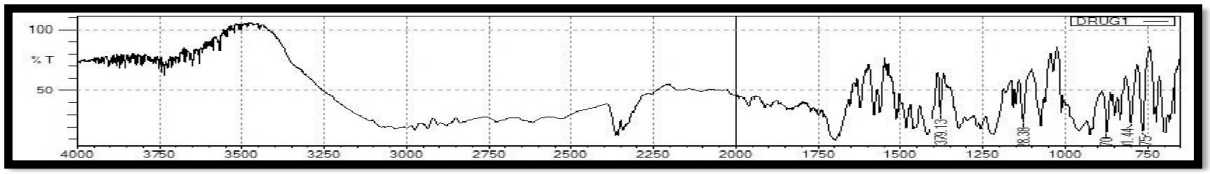

Figure 2: FTIR of flurbiprofen drug sample

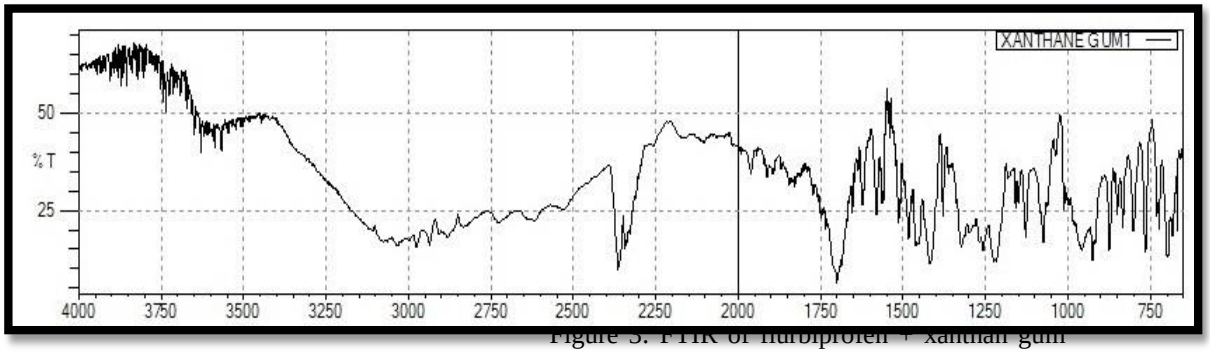

Figure 3: FTIR of flurbiprofen + xanthan gum

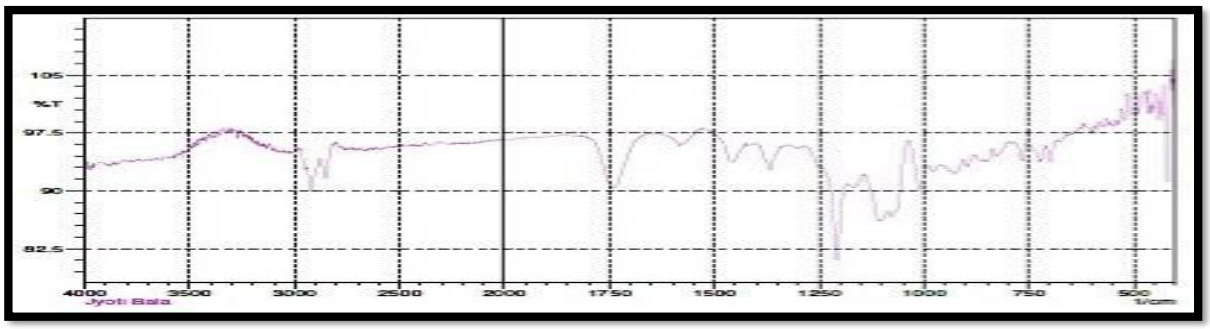

Figure 4: FTIR of flurbiprofen +xanthan gum + liquid paraffin + span 20 + tween 20 + eucalyptus oil + alpha-tocopherol

3. Differential scanning calorimeter (DSC): A thermal analysis of pure flurbiprofen drug was performed. It was performed to observe any physico-chemical interaction between drug and excipients. Thermogram of pure flurbiprofen drug was analyzed by using DSC (Mettler Star SW 12.10) at a heating rate 10°C/minute over a temperature range of 30-300°C. Accurately weighed 2.0-5.0 mg of the sample was hermetically sealed in an aluminum pan. Nitrogen gas was purged at rate of 10 ml/minutes for maintaining inert atmosphere [24-25].

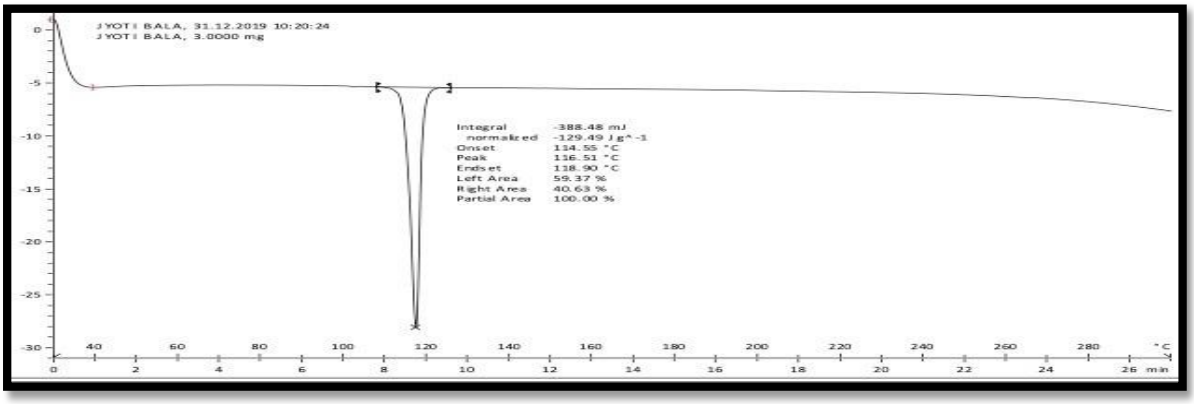

Figure 5: Differential scanning calorimeter of flurbiprofen

4. X-Ray Diffraction (XRD): Powder XRD was performed to check the crystallinity of the drug. The diffraction pattern of pure drug showed its highly crystalline nature as indicated by numerous distinctive peaks at 2θ under following conditions: Ni-filter CU-Kα radiation, 40 KV voltages: 30 mA current, scan speed at 6°C/minutes and scan range 10-80°C.

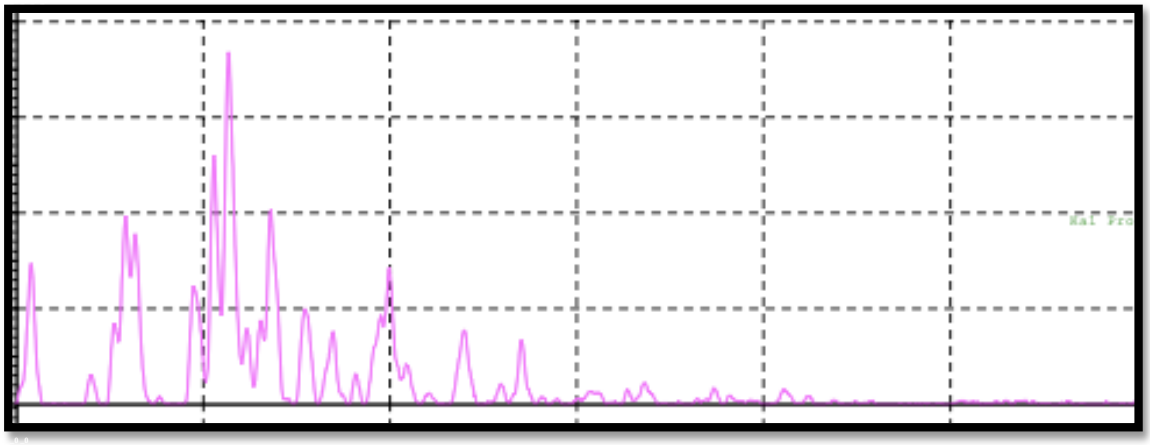

Figure 6: X-Ray Diffraction of flurbiprofen

B. Evaluation of Emulgel

1. Physical appearance: All emulgel formulations were found off white in colour with no phase separation and homogeneous.

2. pH: pH is an important variable for topical preparations to avoid the skin problems the pH of all formulations was found in the range between 4.5-6.5.

3. Homogeneity: All emulgel formulations were tested for homogeneity by spreading a thin layer of emulgel on the glass slide and observed under electronic microscope. Result was shown in figure 7. All emulgel formulations were having the good homogeneity.

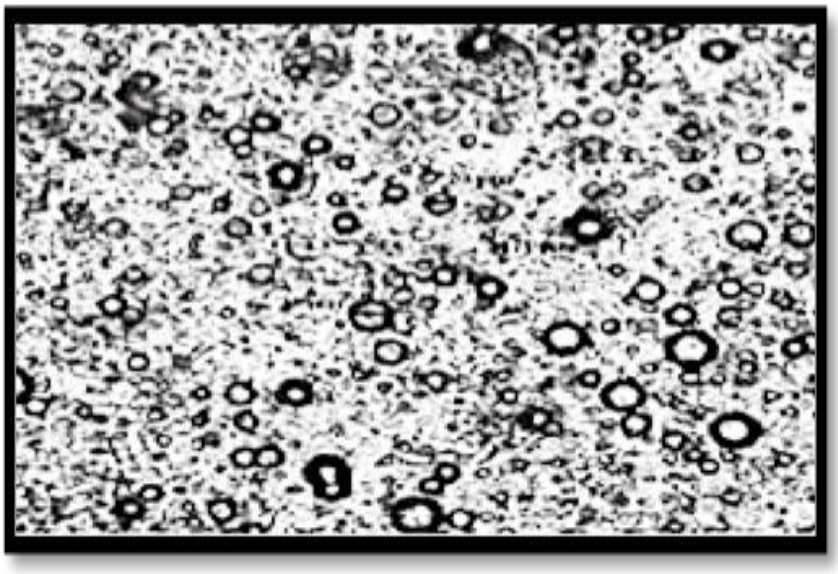

Figure 7: Homogeneity of all formulations

4. Spreadability: The value of spreadability varies from 2.8 to 3.4 cm in diameter, it indicate that the emulgel formulations were easily spreadable by small amount of shear. All emulgel preparations indicated good spreadability. Spreadability of F6 formulation was observed (3.4 cm) which was more than other formulations. It was formulated by using xanthan gum 0.75%.

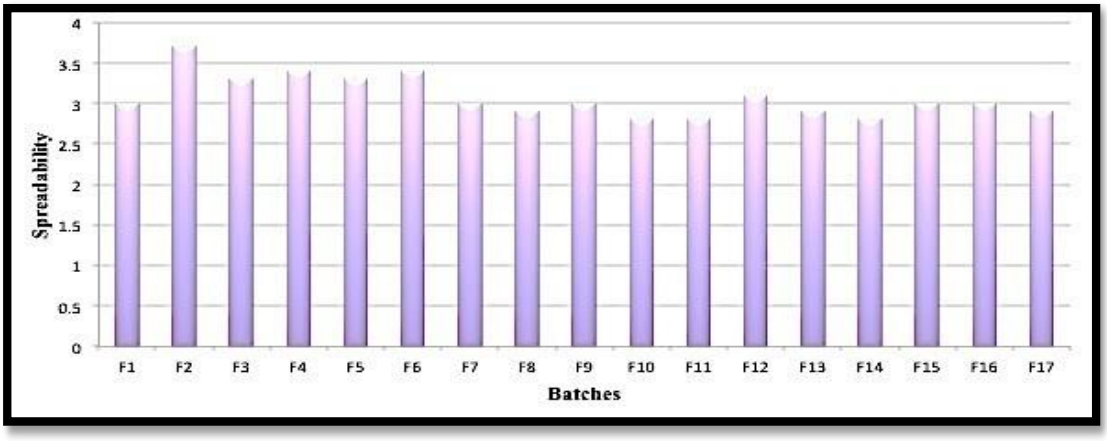

Figure 8: Spreadability of all formulations

5. Extrudability: Extrusion of emulgel from tube is important during its application and in patient acceptance. Extrudability was performed according to the given method and results were shown in figure 9. Extrudability of all formulations was good and compatible.

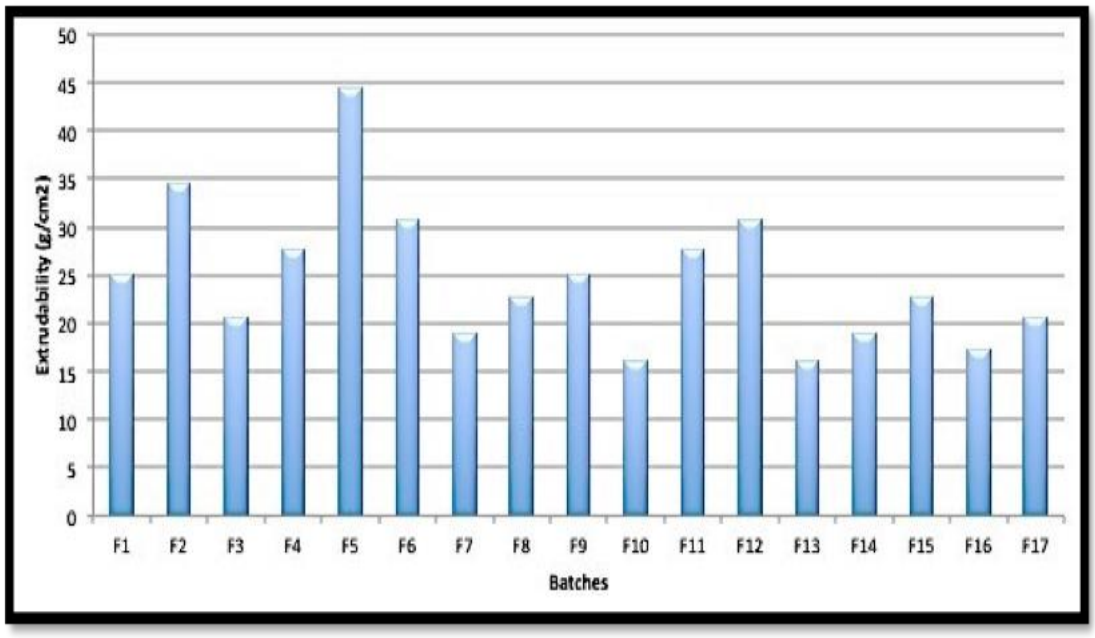

Figure 9: Extrudability of all formulations

6. Viscosity: Viscosity of emulgel formulations was determined by Brookfield programmable viscometer spindle number 4. The spindle was rotated at 10 rpm. Samples of the emulgel were allowed to settle over 30 minutes at the temperature 25°C. The viscosity of the formulations ranged between 2251 to 3067 cps as shown in the figure 10. Among all the formulations F16 prepared by using xanthan gum as gelling agent in the concentration of 1 % has shown more viscosity of 3067 cps and F15 prepared by using gelling agent in the concentration 0.5% has shown very less viscosity.

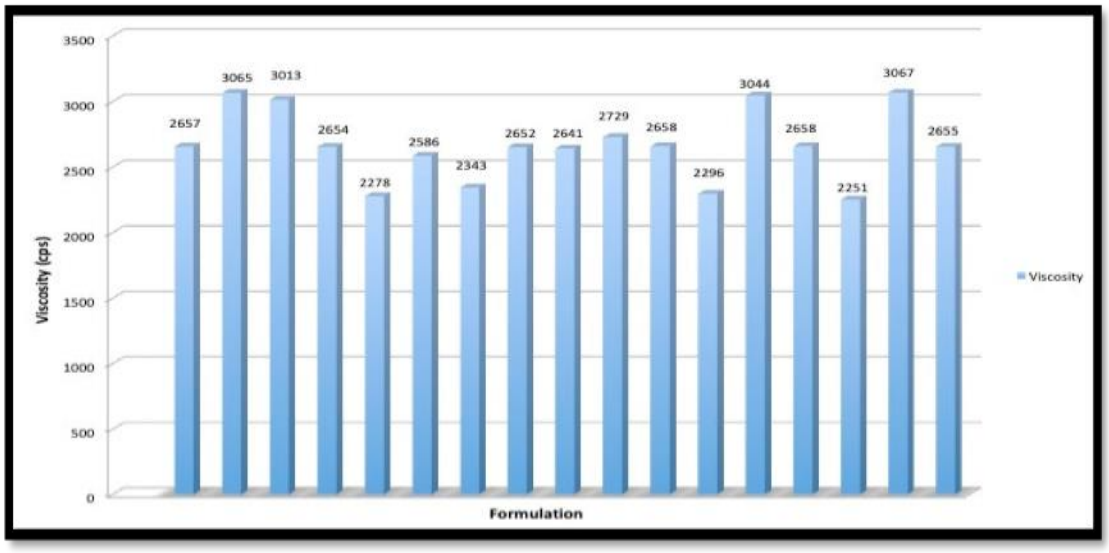

Figure 10: Viscosity of all emulgel formulations

7. Drug content of flurbiprofen: The content of drug in 1gm of emulgel ranged from 81.12 % to 98.61 % as given in Table 4, which indicate that efficient drug loading and uniform distribution of drug in the formulations. F14 (98.61%) formulated by using gelling agent xanthan gum and penetration enhancer eucalyptus oil in the concentration of 0.75 % and 8 % respectively has shown more drug content as compared other formulations.

Table 4: Percentage Drug content of all formulations

Batch no.	Drug content %	Batch no.	Drug content %
F1	96.67 ± 0.69	**F10**	90.74 ± 0.72
F2	93.47 ± 0.26	**F11**	97.21 ± 0.97
F3	92.01 ± 0.13	**F12**	91.33 ± 0.48
F4	98.36 ± 0.50	**F13**	96.20 ± 0.17
F5	84.67 ± 0.58	**F14**	98.61 ± 0.41
F6	94.80 ± 0.42	**F15**	93.74 ± 0.83
F7	81.12 ± 0.38	**F16**	96.93 ± 0.52
F8	95.60 ± 0.74	**F17**	95.33 ± 0.75
F9	96.07 ± 0.85		

8. In-vitro drug release study: In-vitro diffusion studies were performed with cellophane membrane using Franz diffusion cells. Samples were withdrawn periodically and analyzed using UV-VIS double beam spectrophotometer at 247 nm. In-vitro diffusion studies, the formulations F5, F6, F13, F14 and F16 has shown more than 80 % of drug release for 8 hrs.

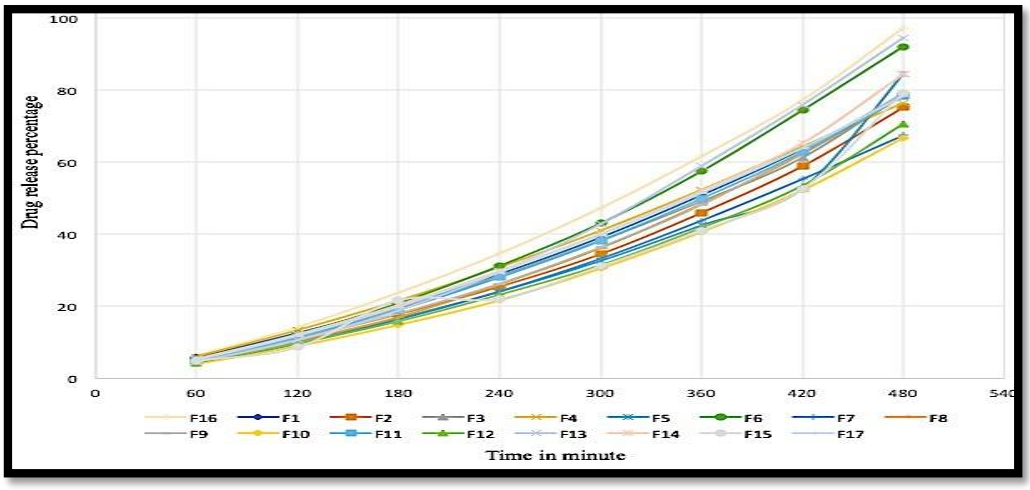

Figure 11: In-vitro drug release study of all emulgel formulations

9. Effect of xanthan gum and eucalyptus oil on percentage drug release:

Final equation in terms of coded factors given below:

% Drug release = +78.362 + 4.28 * A + 9.00625 * B + 4.63125 * C + 3.09 * AB + 2.3 *
AC + 0.9975 * BC + 2.25025 * A^2 + 0.32225 * B^2 + 0.44275 * C^2

The graph reveals the contribution of xanthan gum and eucalyptus oil to percent drug release. The signs of xanthan gum and eucalyptus oil both were positive. The independent and response variable were related using polynomial equation with statistical analysis through Design Expert Software. The values of coefficient X_1, X_2 and X_3 were related to the effect of these variables on the response. The lesser coefficient means the independent variable has more potent influence on the response.

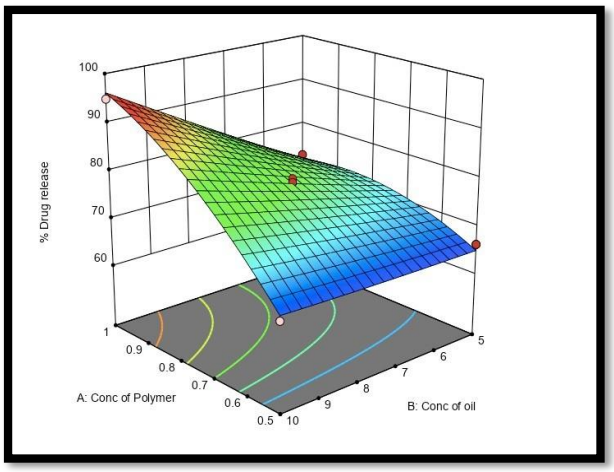

Figure 12: 3D surface response plot of drug release

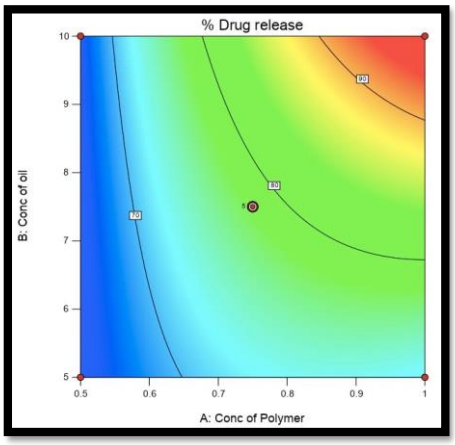

Figure 13: Counter plot of percentage drug release

10. Effect of xanthan gum on viscosity: Viscosity of emulgel shown direct effects on extrudability and release of drug. Xanthan gum was the gelling agent used to increase the consistency of emulgel formulations. By increasing the concentration of polymer in the formulations the viscosity of emulgel was also increased.

Final equation in terms of coded factors given below:

Viscosity = 2703.6 + 350.875 * A + -36.75 * B + -41.625 * C + -11 * AB + 44.75 * AC + 60 * BC + 10.825 * A^2 + -53.925 * B^2 + -88.675 * C^2

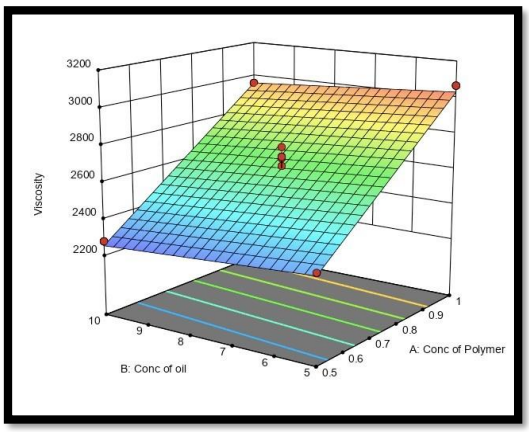

Figure 14: 3D surface response plot of viscosity

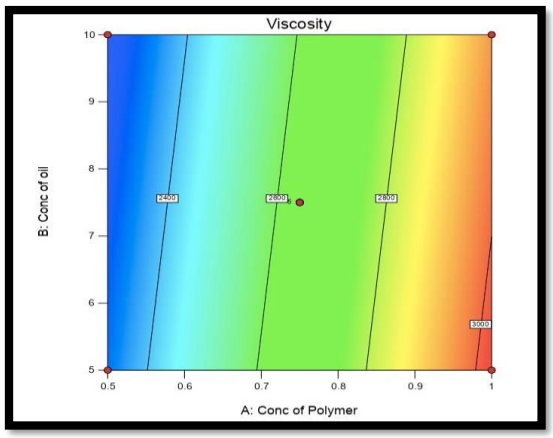

Figure 15: Counter plot of viscosity

11. Stability study of optimized formulation: The optimized formulation was evaluated for physical stability, pH and percentage drug content. Testing carried out by keeping optimized formulations in different storage conditions of 25 ± 3˚C/60 ± 5%RH and 40 ± 3˚C/75 ± 5%RH. Fixed quantity of emulgel was taken out at different time intervals (1 month, 2 months, and 3 months). Stability studies were carried out for F14 formulation for three months.

Table 5: Stability study of optimized formulation under different temperature conditions

Month	Temperature condition (˚C)	Appearance	pH	Drug content (%)
1	25 ± 3˚C/60 ± 5%RH	Off white	5.42 ± 0.23	98.58 ± 0.36
	40 ± 3˚C/75 ± 5%RH	Off white	5.88 ± 0.11	98.62 ± 0.82
2	25 ± 3˚C/60 ± 5%RH	Off white	5.04 ± 0.26	97.88 ± 0.73
	40 ± 3˚C/75 ± 5%RH	Off white	5.31 ± 0.49	98.12 ± 0.28
3	25 ± 3˚C/60 ± 5%RH	Off white	5.78 ±0.19	97.52 ± 0.18
	40 ± 3˚C/75 ± 5%RH	Off white	6.25 ± 0.12	97.19 ± 0.56

VI. Conclusion

Flurbiprofen emulgel was successfully formulated as topical preparation. The oral formulations seem to have adverse effects to avoid such problems topical emulgel was prepared for the delivery of hydrophobic drug. Formulations contained xanthan gum as polymer and eucalyptus oil as penetration enhancer gave superior drug release results. The formulations were optimized by the three factors and two levels Box-Behnken design using Design-Expert software.

The formulations F5, F6, F13, F14 and F16 had shown more than 80 % of drug release for 8 hrs. Drug release affected by the concentration of polymer and penetration enhancer. From this study, it was concluded that the Box-Behnken design had the ability to obtain an optimized formula of viscosity and percentage drug release.

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